UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 08/945,459 | 12/09/1997 | FUSAO MAKISHIMA | 146.1275 | 2741 |

7590 05/27/2003

BIERMAN MUSERLIAN AND LUCAS
600 THIRD AVENUE
NEW YORK, NY 10016

| EXAMINER |
|---|
| ROMEO, DAVID S |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 05/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Applicati n No. | Applicant(s) | |
|---|---|---|---|
| | 08/945,459 | MAKISHIMA ET AL. | |
| | Examin r | Art Unit | |
| | David S Romeo | 1647 | |

*-- The MAILING DATE of this communication appears on th cover she t with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-28 and 41-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-28 and 41-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The amendment filed March 20, 2003 (Paper No. 36) has been entered. Claims 17-28, 41-47 are pending and being examined. Any objection and/or rejection of record that is not maintained and/or repeated in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

***Maintained Formal Matters, Objections, and/or Rejections:***

***Claim Rejections - 35 USC § 103***

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10), Hirel (u20), and Georgiou (x13) and further in view of Tonouchi (y13) and Thompson (a27).

Claims 17, 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10), Hirel (u20), and Georgiou (x13) and further in view of Tonouchi (y13) and Thompson (a27) as applied to claim 17 above and further in view of Hotten (2, cited by Applicants) and Cerletti (n10).

Claims 17-28, 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10), Hirel (u20), and Georgiou (x13) and further in view

of Tonouchi (y13) and Thompson (a27) as applied to claim 17 above and further in view of Hotten (2, cited by Applicants) and Cerletti (n10) as applied to claim 18 above and further in view of Neidhardt (1, cited by Applicants).

Applicant argues that the combination of the prior art made with the benefit of Applicant's teachings would not lead one skilled in the art to Applicant's invention. Applicant's arguments have been fully considered but they are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant's discussion of Celeste and the Wolfman reference has been considered but it is not persuasive. Regardless of the lack of an effect of MP52/GDF-5 in either Celeste or Wolfman, it remains that a chemical composition and its properties are inseparable. Therefore, the properties applicant discloses and/or claims, i.e. "has cartilage and/or bone morphogenetic activity", are necessarily present in the protein taught by the cited prior art. Nor are these properties, i.e. "cartilage and/or bone morphogenetic activity", unexpected because the present specification at page 2, lines 1-3, discloses that the bone morphogenetic activity of MP52 has been reported. Furthermore, Hotten (a37) discloses that in both experimental animals

considerable formation of cartilage and bone was detected in the implants containing [2 to 4 μg] MP52. The corresponding implants with control protein showed no formation whatsoever of cartilage or bone. See column 14, lines 60-64. This response was confirmed in two different assays. See column 16, full paragraph 1, "These results also confirm that MP52 can induce endochondral bone formation."

The comparison of the claimed subject matter with either Celeste or Wolfman is not a comparison with the closest prior art because both Celeste and Wolfman evaluated the induction of tendon/ligament-like tissue at day 10 from implantation. See Celeste at paragraph bridging columns 31-32, and column 32, full paragraph 1. See Wolfman at page 323, Table I. Whereas, as shown in Table 2 in the present specification, the induction of calcified tissue by MP52 was evaluated at day 21 from implantation. The implantation of 1 μg/site or more of the MP52 dimer protein induced calcified tissue in part of the group of the mice, and 10 and more doses induced calcified tissue in all mice used at day 21 from implantation (paragraph bridging pages 15-16). Further, in the rat ectopic assay system the amount of new bone formed and the rate of completion of the bone development progression are dependent upon the amount of BMP-2 implanted. See Wang (u37), page 2221, Table 2. A dose-response and time-course study using the rat ectopic bone formation assay revealed that implantation of 0.5-115 micrograms of partially purified recombinant human BMP-2A resulted in cartilage by day 7 and bone formation by day 14. The time at which bone formation occurred was dependent on the amount of BMP-2A implanted; at high doses bone formation could be observed at 5 days. See Wang (u37), Abstract. Spiro (v37) discloses that matrices loaded with rhGDF-5 induced ectopic cartilaginous and osseous tissue when implanted in subcutaneous or intramuscular sites. In non-human

primate long-bone-defect and spinal-fusion models, rhGDF-5 combined with a mineralized collagen matrix induced bone formation in a manner equivalent to autogenous bone. See the Abstract. Spiro also discloses that GDF-5 has been previously shown to induce ectopic cartilage and bone formation in rodents in vivo, and that, in general, the ectopic bone formation in response to rhGDF-5 was less than that observed with other BMP family members (page 364, right column, last full paragraph). All of the described biological activities of GDF-5 (chondrogenesis, osteogenesis, angiogenesis, etc.) can also be influenced directly by components of the ECM. The synergy demonstrated between components of the ECM and the response to rhGDF-5 can be expected to have a direct impact on the activity and efficacy of matrix/rhGDF-5 combinations in tissue-grafting indications. See page 367, right column, last full paragraph. Given the dependence of the cellular response to rhGDF-5 on an interaction with ECM components, matrix persistence and growth factor concentration become even more important for the performance of a matrix/rhGDF-5 tissue graft (paragraph bridging pages 367-368). Therefore, the differences between either Celeste or Wolfman and the present specification are due to the time at which bone formation was evaluated and the amount of protein implanted. Any differences between either Celeste or Wolfman and the present specification are due to differences in the ways either Celeste or Wolfman and the present specification conducted the assay. Accordingly, the results of either Celeste or Wolfman are insufficient to rebut the prima facie case of obviousness because the assays were conducted in a sufficiently dissimilar manner such that the assays would not provide the same information. Thus, there is no difference between a tendon/ligament-like tissue inducing amount of MP52 and an amount effective to treat cartilage and/or bone diseases. In conclusion, although MP52, like BMP12, possesses

tendon/ligament-like tissue inducing activity, it cannot be fairly said that Celeste teaches that MP52 lacks cartilage and/or bone inducing activity because under the appropriate assay conditions MP52 induces cartilage and/or bone.

Applicant argues that the assumption that shortened forms would be expected to retain activity is an assumption based upon an assumption. Applicant's arguments have been fully considered but they are not persuasive. That shortened forms of rhGDF7 retain activity is a fact rather that an assumption. See the legend of Figure 1A in Wolfman. Celeste clearly teaches that human MP52 proteins containing the amino acid sequence from amino acid #17 or #19 to #119 or #120 of Celeste's SEQ ID NO: 4 are expected to retain activity (column 7, full paragraph 3). This is evidence that one of ordinary skill in the art would expect the shortened forms to retain activity. Applicants have not provided evidence contrary to this teaching or expectation.

Applicant argues that Celeste cannot make a statement on whether shortened forms can induce cartilage or bones. Applicant's arguments have been fully considered but they are not persuasive. Shortened forms are expected to retain activity and there is no evidence of record that these shortened forms would not induce cartilage or bones under the appropriate assay conditions.

Applicant argues that there is no support for the expectation that shortened forms retain activity. Applicant's arguments have been fully considered but they are not persuasive. Celeste clearly teaches that human MP52 proteins containing the amino acid sequence from amino acid #17 or #19 to #119 or #120 of Celeste's SEQ ID NO: 4 are expected to retain activity (column 7, full paragraph 3). This is evidence that one of ordinary skill in the art would expect the shortened forms to retain activity.

Applicant argues that the N-terminus could be important for particular matters and submits Ozkaynak. Applicant's arguments have been fully considered but they are not persuasive. It is acknowledged that Ozkaynak discloses the N-termini of the mature proteins are not conserved that the biological significance of this heterogeneity remains a challenging question (Ozkaynak at page 2091, right column, full paragraph 1). However, this is not evidence that shortened forms of human MP52 do not retain activity. Moreover, obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. Celeste clearly teaches that human MP52 proteins containing the amino acid sequence from amino acid #17 or #19 to #119 or #120 of Celeste's SEQ ID NO: 4 are expected to retain activity (column 7, full paragraph 3). This is evidence that one of ordinary skill in the art would expect the shortened forms to retain activity under the appropriate assay conditions.

Applicant argues that argues that the term "activity" does not indicate that the shortened form must have activity comparable to the original mature MP52, that, theoretically, the remaining activity could not be economically useable, that Celeste does not indicate what activity is retained. Applicant's arguments have been fully considered but they are not persuasive. There is no evidence of record that shortened forms of MP52 do not retain the biological activity of the non-shortened forms, and Celeste is evidence that one of ordinary skill in the art would reasonably expect that the shortened forms of MP52 do retain the biological activity of the non-shortened forms.

***New formal matters, objections, and/or rejections:***

***Specification***

The "Brief Explanation of Drawings" requires revision in order to correspond to the drawing views, e.g. "A", "B", and "C", in the drawings.

Amendments to claims 42, 43, and 47 were indicated in the marked-up copy of the claims attached to the response filed June 24, 2002 (Paper No. 32), but these amendments were not included in the directions to amend the claims. Accordingly, claims 42, 43, and 47 have not been amended as indicated in the marked-up copy of the claims attached to the response filed June 24, 2002.

***Conclusion***

No claims are allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

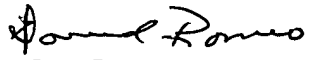
BEFORE FINAL (703) 872-9306
AFTER FINAL (703) 872-9307

IN ADDITION TO THE OFFICIAL RIGHTFAX NUMBERS ABOVE, THE TC 1600 FAX CENTER HAS THE FOLLOWING OFFICIAL FAX NUMBERS: (703) 305-3592, (703) 308-4242 AND (703) 305-3014.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.



DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
MAY 26, 2003